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| EXAMINER |
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1647

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
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Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| | | | |
|------------------------------|--------------------------------|-------------------------------|--|
| Office Action Summary | Application No. 10/520,140 | Applicant(s) BRINES ET AL. | |
| | Examiner Cherie M. Woodward | Art Unit 1647 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 19 December 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-5 and 8-46 is/are pending in the application.
- 4a) Of the above claim(s) 1-5 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 8-46 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 18 July 2005 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group II (claims 6-46) in the reply filed on 19 December 2006 is acknowledged. The traversal is on the grounds that claim 1 is not anticipated by Vandenberg, US PreGrant Publication US 2003/0118547 (published 26 June 2003, priority to 25 January 2001). Applicant argues that Vandenberg does not teach a composition comprising an anti-inflammatory agent and erythropoietin, as recited in claim 1. This is not found persuasive because Vandenberg teaches the administration of a pharmaceutical composition comprising erythropoietin (p. 6, paragraph 0076) [a tissue protective cytokine], and an anti-inflammatory agent (p. 4 and 6, paragraphs 0033 and 0074) in a pharmaceutically acceptable carrier (p.9, paragraph 0106). The composition of claim 1 is known in the art and is not novel. Thus, the remaining claims lack the special technical feature.

The requirement is still deemed proper and is therefore made FINAL.

Formal Matters

2. Claims 1-5, 8-46 are pending. Claims 6-7 and 47-52 have been cancelled by Applicant. Claims 1-5 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 19 December 2006. Claims 8-46 are under examination.

Claim Objections

3. Claim 39 is objected to because of the following informalities: the claim recites "the methods of claim 38...". However, claim 38 recites only one method. The plurality of the word "methods" is objected to. Appropriate correction is required.

Specification - Objection

4. The use of the trademarks SIGMA (p. 112), ORTHO BIOTECH (p. 113) and DULBECCO (p. 114), for example, have been noted in this application. Trademarks should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Applicant is requested to thoroughly review the entire specification and correct the capitalization of all trademarks therein.

5. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

6. The disclosure is objected to because of the following informalities: the phrase "TNF-__" is found on page 115, paragraph 323, lines 3 to 4. It is unclear whether the underlined portion is a typographical error or whether a greek symbol, alpha, for example, (i.e. TNF- α) was supposed to be present.

Appropriate correction is required.

Priority/Benefit

7. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 365(c) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35

U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 10/188,905, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The instant claims under examination (8-46) are drawn to a method of treating inflammation in a mammal by administering a composition comprising a tissue protective cytokine, and a pharmaceutically acceptable carrier and one or more anti-inflammatory agents or immunomodulatory agents. The subject matter of instant claims 8-46 could not be found in the originally filed claims or specification of US Application 10/188,905. As such, benefit is granted to the International filing date of 3 July 2003.

Claim Rejections - 35 USC § 112, First Paragraph

Scope of Enablement

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 8-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling in the art for a method of treating inflammation in a mammal comprising administering recombinant Epoetin Alpha in an isotonic sodium chloride solution with glucocorticoids or IFN- β , does not reasonably provide enablement for a method of treating inflammation in a mammal comprising administering a generic tissue protective cytokine, and a pharmaceutically acceptable carrier and one or more anti-inflammatory agents or immunomodulatory agents. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability, 5) existence of working samples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of

experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims recite a method treating inflammation in a mammal comprising responsive cells, tissues, and/or organs, said method comprising administering to a mammal in need thereof a pharmaceutical composition comprising a prophylactically or therapeutically effective amount of a tissue protective cytokine and a pharmaceutically acceptable carrier, and administering to the mammal a prophylactically or therapeutically effective amount of one or more anti-inflammatory agents or immunomodulatory agents; wherein the anti-inflammatory agent is selected from the group consisting of a corticosteroid, a glucocorticoid, a steroid, a non-steroidal anti-inflammatory drug, a beta-agonist, a anticholinergic agent, a methyl xanthine, gold injection, a sulphasalazine, penicillamine, a anti-angiogenic agent, dapsone, psoralen, a anti-malarial agent, a anti-viral agent, and an antibiotic; wherein the immunomodulatory agent is selected from the group consisting of a proteinaceous agent, a peptide mimetic, an antibody, a nucleic acid molecule, a small molecule, an organic compound, an inorganic compound, methothrexate, leflunomide, cyclophosphamide, cytoxan, immuran, cyclosporine A, minocycline, azathioprine, an antibiotic, methylprednisolone (MP), a corticosteroid, a steroid, mycophenolate mofetil, rapamycin, mizoribine, deoxyspergualin, brequinar, a malononitriloamine, a T cell receptor modulator, and a cytokine receptor modulator; wherein said tissue protective cytokine is i) an erythropoietin that lacks sialic acid moieties; ii) an erythropoietin that lacks N-linked or lacks O-linked carbohydrates; iii) an erythropoietin having a reduced carbohydrate content by treatment of native erythropoietin with at least one glycosidase; iv) an erythropoietin having at least one or more oxidized carbohydrates; v) an erythropoietin comprising at least one or more oxidized carbohydrates which is chemically reduced; vi) an erythropoietin comprising at least one or more modified arginine residues; vii) an erythropoietin comprising at least one or more modified lysine residues or a modification of the N-terminal amino group of the erythropoietin molecule; viii) an erythropoietin comprising at least a modified tyrosine residue; ix) an erythropoietin comprising at least a modified aspartic acid or a glutamic acid residue; x) an erythropoietin comprising at least a modified tryptophan residue; xi) an erythropoietin having at least one amino group removed; xii) an erythropoietin comprising at least an opening of at least one of the cysteine linkages in the erythropoietin molecule; and xiii) a truncated erythropoietin; wherein

Art Unit: 1647

said tissue protective cytokine is asialoerythropoietin or phenylglyoxal-erythropoietin; wherein the tissue protective cytokine is capable of traversing an endothelial cell barrier; wherein the endothelial cell barrier is selected from the group consisting of blood-brain barrier, blood-eye barrier, blood-testis barrier, blood-ovary barrier, and blood-uterus barrier; wherein responsive cells, tissues, and/or organs in the mammal, are selected from the group consisting of neuronal cells, muscle cells, heart, lung, liver, kidney, small intestine, adrenal cortex, adrenal medulla, capillary cells, endothelial cells, testes, ovary, endometrial cells, and stem cells; wherein the responsive mammalian cells further comprise cells selected from the group consisting of photoreceptor cells, ganglion cells, bipolar cells, horizontal cells, amacrine cells, Muieller cells, myocardium cells, pace maker cells, sinoatrial node cells, sinoatrial node cells, sinus node cells, atrioventricular node cells, bundle of His cells, hepatocyte cells, stellate cells, Kupffer cells, mesangial cells, goblet cells, intestinal gland cells, enteral endocrine cells, glomerulosa cells, fasciculate cells reticularis cells, chromaffin cells, pericyte cells, Leydig cells, Sertoli cells, sperm cells, Graffian follicle cells, primordial follicle cells, endometrial stroma cells, and endometrial cells; wherein said tissue protective cytokine is asialoerythropoietin; wherein said asialoerythropoietin is human asialoerythropoietin; wherein said tissue protective cytokine is an erythropoietin with no N-linked carbohydrates; wherein said tissue protective cytokine is an erythropoietin with no O-linked carbohydrates; wherein said tissue protective cytokine is an erythropoietin treated with at least one glycosidase; wherein said tissue protective cytokine is periodate-oxidized erythropoietin; wherein said periodate-oxidized erythropoietin is chemically reduced with sodium cyanoborohydride; wherein said tissue protective cytokine is an erythropoietin comprising a R-glyoxal moiety on the one or more arginine residues, wherein R is aryl or alkyl moiety; wherein said erythropoietin is phenylglyoxal-erythropoietin; wherein said tissue protective cytokine is an erythropoietin in which at least one arginine residue is modified by reaction with a vicinal diketone selected from the group consisting of 2,3-butanedione and cyclohexanedione; wherein said tissue protective cytokine is an erythropoietin in which at least one arginine residue is reacted with 3-deoxyglucosone; wherein said tissue protective cytokine is an erythropoietin molecule comprising at least one biotinylated lysine or N-terminal amino group; wherein said erythropoietin molecule is biotinylated erythropoietin; wherein said tissue protective cytokine is a glucitolyl lysine erythropoietin or a fructosyl lysine erythropoietin;

Art Unit: 1647

wherein said tissue protective cytokine is an erythropoietin having at least one carbamylated lysine residue; wherein said carbamylated erythropoietin is selected from the group consisting of alpha-N-carbamoylerythropoietin, N-epsilon-carbamoylerythropoietin, alpha-N-carbamoyl, N-epsilon-carbamoylerythropoietin, alpha-N-carbamoylasialoerythropoietin, N-epsilon-carbamoylasialoerythropoietin, alpha-N-carbamoyl, N-epsilon-carbamoylasialoerythropoietin, alpha-N-carbamoylhyposialoerythropoietin, N-epsilon-carbamoylhyposialoerythropoietin, and alpha-N-carbamoyl N-epsilon-carbamoylhyposialoerythropoietin; wherein said tissue protective cytokine is an erythropoietin in which at least one lysine residue is acylated; wherein a lysine residue of said erythropoietin is acetylated; wherein said acetylated erythropoietin is selected from the group consisting of alpha-N-acetylerythropoietin, N-epsilon-acetylerythropoietin, alpha-N-acetyl, N-epsilon-acetylerythropoietin, alpha-N-acetylasialoerythropoietin, N-epsilon-acetylasialoerythropoietin, alpha-N-acetyl, N-epsilon-acetylasialoerythropoietin, alpha-N-acetylhyposialoerythropoietin, N-epsilon-acetylhyposialoerythropoietin, and alpha-N-acetyl, N-epsilon-acetylhyposialoerythropoietin; wherein said tissue protective cytokine is an erythropoietin comprising a succinylated lysine residue; where said erythropoietin is selected from the group consisting of alpha-N-succinylerythropoietin, N-epsilon-succinylerythropoietin, alpha-N-succinyl, N-epsilon-succinylerythropoietin, alpha-N-succinylasialoerythropoietin, N-epsilon-succinylasialoerythropoietin, alpha-N-succinyl, N-epsilon-succinylasialoerythropoietin, alpha-N-succinylhyposialoerythropoietin, N-epsilon-succinylhyposialoerythropoietin, and alpha-N-succinyl, N-epsilon-succinylhyposialoerythropoietin; wherein said tissue protective cytokine is an erythropoietin with at least one lysine residue modified by a 2,4,6-trinitrobenzenesulfonic acid salt; wherein the salt is 2,4,6-trinitrobenzenesulfonate sodium; wherein said tissue protective cytokine is an erythropoietin in which at least one tyrosine residue is nitrated and/or iodinated; wherein said tissue protective cytokine is an erythropoietin in which an aspartic acid and/or glutamic acid residue is reacted with a carbodiimide followed by reaction with an amine; wherein said amine is glycineamide; wherein the inflammation results from a disease condition or trauma; wherein the trauma is selected from the group consisting of angitis, chronic bronchitis, pancreatitis, osteomyelitis, rheumatoid arthritis, glomerulonephritis, optic neuritis, temporal arteritis, encephalitis, meningitis, transverse myelitis, dermatomyositis, polymyositis, necrotizing fasciitis, hepatitis, and necrotizing enterocolitis; wherein the tissue

protective cytokine inhibits inflammation resulting from cytokines produced by glial cells; wherein the inflammation is triggered by apoptosis.

The nature of the invention is drawn to a method of treating inflammation in a mammal by administering erythropoietin or an erythropoietin derivative or analog and a pharmaceutically acceptable carrier and administering to the mammal one or more anti-inflammatory agents or immunomodulatory agents.

The state of the art discloses methods of treating inflammation due to blunt force trauma injury with a composition comprising recombinant Epoetin alpha (PROCRIT) in an isotonic sodium chloride/sodium citrate and administration of glucocorticoids or IFN β (Brines et al., PNAS USA, 2000 Sept 12; 97(19):10526-10531, especially at p. 10526, column 2, second paragraph; p. 10529, column 2, second paragraph; p. 10530, column 1, second paragraph; and p. 10531, column 2, second paragraph.) Kitajima et al., (Rinsho Ketsueki. 1994 Jul. 35(7):694-8, Abstract Only), teach a method of treating inflammation using recombinant EPO, Cepharanthin, and low dose prednisone. Vandenberg, (US PreGrant Publication US 2003/0118547, published 26 June 2003, benefit to 25 January 2001) teaches the administration of a pharmaceutical composition comprising erythropoietin (p. 6, paragraph 0076) [a tissue protective cytokine], and an anti-inflammatory agent (p. 4 and 6, paragraphs 0033 and 0074) in a pharmaceutically acceptable carrier (p.9, paragraph 0106). Lin (US Patent 5,621,080) teaches methods of making recombinant EPO (column 13, line 60-column 14, line 67 and Examples). Lin teaches methods of making recombinant EPO in insect cells (column 36, lines 57-61). Lin teaches methods of administering recombinant EPO to mammals (claims). Satake et al., (Biochimica et Biophysica Acta. 1990;1038:125-129) teach an embodiment of erythropoietin having at least one or more modified lysine residues or a modification of the N-terminal amino group of the erythropoietin molecule, which is highly active. Satake et al. teach that guanidination of amino groups of the lysine residues yielded derivatives that showed higher biological activities *in vitro* than native recombinant human EPO (abstract, page 127, paragraphs four and five).

The level of skill of those in the art is high due in part to the unpredictability of the biological function of proteins with altered amino acid or glycosylation structures. The assertion that the disclosed erythropoietin variants have biological activities similar to known recombinant Epoetin alpha cannot be accepted in the absence of supporting evidence, because the

Art Unit: 1647.

relevant literature reports examples of polypeptide families wherein individual members have distinct, and sometimes even opposite, biological activities. For example, Tischer et al. (U.S. Patent 5,194,596) establishes that VEGF (a member of the PDGF, or platelet-derived growth factor, family) is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells, which is opposite to the mitogenic activity of naturally occurring PDGF which is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (column 2, line 46 to column 3, line 2). The differences between PDGF and VEGF are also seen *in vivo*, wherein endothelial-pericyte associations in the eye are disrupted by intraocular administration of PDGF but accelerated by intraocular administration of VEGF (Benjamin et al., 1998, Development 125:1591-1598; see Abstract and pp. 1594-1596). In the transforming growth factor (TGF) family, Vukicevic et al. (1996, PNAS USA 93:9021-9026) disclose that OP-1, a member of the TGF- β family of proteins, has the ability to induce metanephrogenesis, whereas closely related TGF- β family members BMP-2 and TGF-1 had no effect on metanephrogenesis under identical conditions (p. 9023, paragraph bridging columns 1-2). See also Massague, who reviews other members of the TGF- β family (1987, Cell 49:437-8, esp. p. 438, column 1, second full paragraph to the end). Similarly, PTH and PTHrP are two structurally closely related proteins which can have opposite effects on bone resorption (Pilbeam et al., 1993, Bone 14:717-720; see p. 717, second paragraph of Introduction). Finally, Kopchick et al. (U.S. Patent 5,350,836) disclose several antagonists of vertebrate growth hormone that differ from naturally occurring growth hormone by a single amino acid (column 2, lines 37-48).

The specification states that the present invention relates to tissue protective cytokines generated by the chemical modification of erythropoietin and their uses on erythropoietin-responsive and associated cells (p. 2, paragraph 6). The specification does not teach erythropoietin as a tissue protective cytokine, but rather, teaches erythropoietin as an inducer of tissue protective cytokines (see p. 2, paragraph 6). No cytokines are taught in the specification that are induced by administration of erythropoietin and anti-inflammatories or immunomodulatory agents, such that a person of ordinary skill in the art would know and understand which cytokines were designated by Applicant as "tissue protective cytokines."

Applicant is not enabled for the method comprising the genus of tissue protective cytokines generated by the chemical modification of erythropoietin. Applicant fails to name

these “tissue protective” cytokines, and, as such, fails to provide structural or functional information such that one of ordinary skill in the art would know what Applicant means by the phrase “tissue protective cytokines.” Without knowing which cytokines Applicant is referring to, a person of ordinary skill in the art would have to engage in undue experimentation to determine which cytokines exhibit a tissue-protective function.

It is unclear how the tissue protective cytokines of the claimed method would treat inflammation in a manner different from treatment with one or more anti-inflammatory agents or immunomodulatory agents. It is noted that the specification does not define what constitutes inflammation. As such, the plain ordinary meaning of inflammation is used by the Examiner (see also, Steadman’s Medical Dictionary, 27th Ed. 2000, Lippincott, Williams, and Wilkins). The specification fails to disclose a synergistic effect of a tissue protective cytokine administered with one or more anti-inflammatory agents or immunomodulatory agents. No unexpected results are taught and no reasons are provided such that one of ordinary skill in the art would understand why it is important to administer a tissue protective cytokine along with a well known, effective anti-inflammatory agent, such as aspirin, ibuprophen, a COX-2 inhibitor, NSAID, steroid, or biologic, such as a TNF α inhibitor. Because no guidance is provided, the results of administering both a tissue protective cytokine and an anti-inflammatory agent or immunomodulatory agent would be unpredictable beyond the known effects of known anti-inflammatory agents or known immunomodulatory agents. Undue experimentation would be required to determine what effects, if any, resulted from the prior, concurrent, co-administration, or subsequent administration of a tissue protective cytokine and an anti-inflammatory agent or immunomodulatory agent, regardless of the structural modifications made to the tissue protective cytokine, such as erythropoietin.

A review of the language of the claim indicates that these claims are drawn to many different genera, i.e., the genus of mammals comprising responsive cells, tissues and/or organs; the genus of tissue protective cytokines, the genus of anti-inflammatory agents, the genus of immunomodulatory agents, the genus of anti-malarial agents, the genus of anti-viral agents, the genus of antibiotics, the genus of non-steroidal anti-inflammatory agents, the genus of anti-angiogenic agents, the genus of beta-agonists, the genus of proteinaceous agents, the genus of peptide mimetics, the genus of antibodies, the genus of nucleic acid molecules, the genus of

small molecules, the genus of organic compounds, the genus of inorganic compounds, the genus of T-cell receptor modulators, the genus of cytokine receptor modulators, the genus of recombinantly produced erythropoietin, the genus of disease conditions, and the genus of traumas. The instant claims are not supported by an enabling disclosure that provides guidance on how to make or use the claimed invention comprising members of the aforementioned genera of agents, to treat the genus of mammals, with a generic recitation of disease conditions and/or traumas. It would be unpredictable for one of skill in the art to determine whether the claimed method would have an anti-inflammatory effect on the cells, tissue, and/or organs of different mammals without knowing which mammals were so indicated for the method of treatment, the treatment to be administered, and the treatment dosages or at the very least, dose ranges, such that the claimed method could be practiced without undue experimentation.

Additionally, the instant claims are not supported by an enabling disclosure for a prophylactically effective amount of tissue protective cytokine. Prevention involves “attacking” the underlying cause of a disorder. In this case a person of skill in the art would have to know the amount or range of administration for a tissue protective cytokine to administer to prevent any type of inflammation in any mammal, regardless of the mechanisms which give rise to the inflammatory disorder. The skilled artisan is aware that the causes of inflammation are multivariate and not all of the causes for every type of inflammation were unknown at the time of the instant invention. For purposes of enablement, the specification must provide reasonable detail in order for those skilled in the art to carry out the invention. In this case, the specification must disclose a dosage amount that prevents inflammation in mammals, regardless of the underlying causes of the inflammation. The teachings of the specification do not enabled a person of ordinary skill in the art to make and use the claimed method comprising administration of a prophylactically effective amount of a tissue protective cytokine. Moreover, “[p]atent protection is granted only in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable.” *Genentech Inc. v. Novo Nordisk A/S*, 108 F.3d at 1366, 42 USPQ2d at 1005 (Fed. Cir.), cert. denied, 118 S. Ct. 397 (1997), (“Tossing out the mere germ of an idea does not constitute an enabling disclosure”).

Additionally, no dosage information is provided such that one of ordinary skill in the art would know what a prophylactic or therapeutic dose of a tissue protective cytokine would be.

Although effective treatment dosages for recombinant erythropoietin are known in the art, the US Food and Drug Administration recently released an FDA Alert (16 November 2006, updated 16 February 2006 and 9 March 2007) regarding use of recombinant EPO in cancer patients when the drug is used in an unapproved dosage. The FDA Alert noted serious and life-threatening side effects when unapproved dosages were used (see FDA Alert). In light of the art, it would be unpredictable to determine the dose ranges for administration of a tissue protective cytokine in a prophylactically or therapeutically effective amount to treat inflammation, as recited in the claims. Undue experimentation would be required to determine the prophylactic and therapeutically effective dosages mammalian species (as claimed). Routine dose optimization would not be predictive in light of the FDA Alert.

The instant claims are not supported by an enabling disclosure. Satake et al., (*supra*) teach that modification of lysine residues to neutral or negative charges, such as in acetylation, trinitrophenylation, carbamylation or succinylation cause a significant loss of recombinant human erythropoietin activity. Satake *et al.* also teach that the biological activity of recombinant human erythropoietin (EPO) is sensitive to chemical modifications of lysine residues (abstract and page 127, paragraphs two and three, Table 1 and page 128, Discussion). The instant specification fails to demonstrate biological activity of EPO having at least one or more modified lysine residues, for instance neutral or negative charges to lysine residues, which are as effective as unmodified EPO. The instant specification fails to teach the administration of the instant lysine-modified EPO to mammals. The specification need not contain an example if the claimed invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation. Lack of working examples, however is a factor to be considered, especially in a case involving an unpredictable and undeveloped art. In this case, the art is unpredictable based on the evidence provided. One skilled in the art cannot readily anticipate the effect of the claimed invention, the experimentation is not routine and Applicant has provided no guidance.

Claim 11 recites essentially any EPO produced recombinantly, in bacteria, yeast, insect cells, or in mammalian cells where the amount of sugar in the medium is altered, or treated with glycosidase, or having oxidized carbohydrates. Fukada et al., (Blood. 1989 Jan;73(1):84-9, Abstract Only) teach that sialic acid of recombinant erythropoietin is necessary for EPO to

circulate stably. Fukada et al., also teach that glycoproteins with more than three lactosaminyl repeat units may be cleared by the galactose binding protein of hepatocytes (abstract). Thus, it appears that not all forms of recombinantly produced EPO are biologically functional. As such, it would require undue experimentation for a person of ordinary skill in the art to make and test every recombinant EPO variant produce in bacteria, yeast, insect cells, or mammalian cells that have altered amino acid or glycosylation patterns and test the same for activity.

Further, there is insufficient guidance in the specification to support the breadth of claims 43 and 44, which are drawn to a method of treating a inflammation where the inflammation results from a disease condition or trauma. The inflammation that results from a disease condition or trauma is unpredictable in different species. The specification fails to provide guidance on the requisite degree of inflammation needed to characterize a “disease condition” or trauma. For example, the breadth of Applicant’s claims encompass a method of administering modified EPO and aspirin to treat a paper cut. There is no support in the specification to show that Applicant’s method will be effective for treating a paper cut or that aspirin, alone, is insufficient to treat the inflammation arising from the trauma of a paper cut.

Applicant fails to provide any working examples of *in vivo* use of the claimed method, as written, and only one, *in vitro* method is exemplified. Although working examples are not required, they are considered helpful in determining the predictability and the amount of experimentation necessary to make or use the invention, as claimed. The examples in the specification are drawn to: the distribution of the EPOR in the human brain (Example 1, p. 87); how to make a variety of post-translationally modified or chemically altered recombinant EPO (Examples 2 and 3, pp. 89-99); administration of modified recombinant EPO in mice reciting a neuroprotective effect (Example 4, pp. 100-102); EPO crossing the blood-cerebrospinal fluid tight barrier (Example 5, p. 102); maintenance of function in a heart prepared for transplantation (Example 6, pp. 102-104); EPO protein protecting myocardium from ischemic injury (Example 7, p. 104); protection of retinal ischemia by peripherally administered EPO (Example 8, pp. 104-105); restorative effects of EPO on diminished cognitive function arising from brain injury (Example 9, p. 106); induction of stroke using a kainate model (Example 10, pp. 106); spinal cord injury models (Example 11, pp. 107-109); middle cerebral artery occlusion studies used to show anti-inflammatory effects of EPO administered alone in male rats, compared to

administration of PBS (Example 12A, pp. 110-112); and an acute experimental allergic encephalomyelitis (EAE) in Lewis rats used to show anti-inflammatory effects of EPO administered with serum albumin, compared to controls who received PBS and serum albumin (Example 12B, pp. 112-113). In vitro studies of primary cultures of glial cells treated with trimethyltin (TMT) in the presence or absence of recombinant human EPO are taught at p. 114-115.

There are no working examples of a method of treating inflammation in a mammal *in vivo* comprising administering a tissue protective cytokine and a pharmaceutically acceptable carrier and administering to the mammal one or more anti-inflammatory or immunomodulatory agents. The trimethyltin (TMT) of Example the in vitro studies on pp. 114-115 could be considered an “immunomodulatory agent” using Applicant’s definition of immunomodulatory agent on page 16 of the specification, wherein an immunomodulatory agent in a particular embodiment is selected from the group consisting of, among others recited compositions, a peptide mimetic, a small molecule, an organic compound, and an inorganic compound. Applicant is permitted to be his own lexicographer. However, Applicant’s definition is so exceptionally broad as to be repugnant in the art because the definition provided on page 16 of the specification encompass everything under the sun as an immunomodulatory agent. Additionally, it is so overly broad as to encompass agents that are immunologically inert, such as a ceramic composition, and as such, would not be effective as immunomodulatory agents. Because Applicant’s broad definition of immunomodulatory agent in the particular embodiment recited on page 16, encompasses mutually exclusive compositions, little weight is given to the “immunomodulatory agent” of the examples of in vitro studies on pp. 114-115. Further, Trimethyltin (TMT) is a class of organic chemical compounds that are neurotoxins used to induce damage in the limbic system, cerebral cortex, and the brainstem (see, i.e. Gunaseker et al., Toxicological Sciences. 2001; 64:83-89, especially p. 83). The *in vitro* studies example, reciting primary cultured glial cells on pp. 114-115 of the specification, enables Applicant’s claims insofar as it teaches a method of inducing and attempting to concurrently attempting to suppress inflammation in *in vitro* primary cultures of glial cells from new born Sprague-Dawley rats 1-2 days old comprising administering 1 µg of Trimethyltin (TMT) in the presence of recombinant human EPO (Epoetin alpha, brand name PROCRIT) at a dosage of 10U (80ng/ml) (pp. 114-115).

No examples are provided of an *in vivo* method of treating inflammation in a whole, living mammal comprising administering a tissue protective cytokine and a pharmaceutically acceptable carrier and administering to the mammal one or more anti-inflammatory or immunomodulatory agents. The examples provided in the disclosure also fail to show administration (in vivo or in vitro) of anything other than commercially available recombinant human EPO as Epoetin alpha, brand name PROCRIT). Applicant does not have any examples of administering the claimed modified recombinant EPO variants *in vivo* or *in vitro*. There is no teaching in the specification showing that these modified recombinant EPO variants would be biologically functional for the recited purpose in mammals. As such, use of the various modified recombinant EPO variants in mammals would be unpredictable and it would require undue experimentation to determine whether they have an anti-inflammatory effect in mammals.

Due to the large quantity of experimentation necessary to generate the derivatives recited in the claims and screen same for activity for use in the claimed method, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention and the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112, First Paragraph

Written Description

10. Claims 8-46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The claims recite as stated, *supra*. *Vas-Cath Inc. V. Mahurkar*, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117). A review of the language of the claim indicates that these claims are drawn to many different genera, i.e., the genus of mammals comprising responsive cells, tissues and/or organs; the genus of tissue protective cytokines, the genus of anti-inflammatory agents, the genus of immunomodulatory agents, the genus of anti-malarial agents, the genus of anti-viral agents, the genus of antibiotics, the genus of non-steroidal anti-inflammatory agents, the genus of anti-angiogenic agents, the genus of beta-agonists, the genus of proteinaceous agents, the genus of peptide mimetics, the genus of antibodies, the genus of nucleic acid molecules, the genus of small molecules, the genus of organic compounds, the genus of inorganic compounds, the genus of T-cell receptor modulators, the genus of cytokine receptor modulators, the genus of recombinantly produced erythropoietin, the genus of disease conditions, and the genus of traumas.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In *Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that, while applicants are not required to disclose every species encompassed by a genus, the description of the genus is achieved by the recitation of a representative number of species falling within the scope of the claimed genus. At section B(1), the court states, "An adequate written description of a DNA ... requires a precise definition, such

as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention.”

In the claimed genus of mammals, only the species of rats, mice, and human cells *in vitro*, are described. In the claimed genus of tissue protective cytokines, only erythropoietin is described, but is described as being the inducer of tissue protective cytokines (see p. 2, paragraph 6). In the claimed genus of anti-inflammatory agents, other subgenera of agents are described, such as corticosteroids, glucocorticoids, and NSAIDS (non-steroidal anti-inflammatory drugs) (p. 13). In the claimed genus of immunomodulatory agents, methotrexate, and the subgeneras of T-cell modulators and cytokine receptor modulators are described (p. 14). The genres of organic compounds, inorganic compounds, disease conditions and traumas are inadequately described and no species are described for the claimed genus of anti-malarial agents, anti-viral agents, antibiotics, non-steroidal anti-inflammatory agents, anti-angiogenic agents, beta-agonists, proteinaceous agents, peptide mimetics, antibodies, nucleic acid molecules, small molecules, T-cell receptor modulators, or cytokine receptor modulators. The disclosure of a single disclosed species may provide an adequate written description of a genus when the species disclosed is representative of the genus. However, the present claim encompasses numerous species that are not further described.

In the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed genus, which is the genus of mammals comprising responsive cells, tissues and/or organs; the genus of tissue protective cytokines, the genus of anti-inflammatory agents, the genus of immunomodulatory agents, the genus of anti-malarial agents, the genus of anti-viral agents, the genus of antibiotics, the genus of non-steroidal anti-inflammatory agents, the genus of anti-angiogenic agents, the genus of beta-agonists, the genus of proteinaceous agents, the genus of peptide mimetics, the genus of antibodies, the genus of nucleic acid molecules, the genus of small molecules, the genus of organic compounds, the genus of inorganic compounds, the genus of T-cell receptor modulators, the genus of cytokine receptor modulators, the genus of recombinantly produced erythropoietin, the genus of disease conditions, and the genus of traumas. One of skill in the art would not recognize from the disclosure that the applicant was in possession of the genus. The specification

Art Unit: 1647

does not clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed (see *Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112, Second Paragraph

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 8, 43, and 44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim recites the method of claim 43 wherein the trauma is selected from the recited group. However, the group consists of inflammatory diseases, all ending in the traditional “-itis” ending. These conditions are chronic and acute inflammatory diseases, but they are not traumas. Applicant may act as his or her own lexicographer, however the word “trauma” is not otherwise defined in the specification, and as such, it is given its plain ordinary meaning (see i.e. Steadman’s Medical Dictionary, 27th Ed., 2000 Lippincott Williams & Wilkins).

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 8-11, 12-16, 19-20, 28-29, and 43-46 are rejected under 35 U.S.C. 102(b) as being anticipated by Brines et al., (PNAS USA, 2000 Sept 12; 97(19):10526-10531).

The claims recite as stated, *supra*. Brines et al., discloses methods of treating inflammation due to blunt force trauma injury with a composition comprising recombinant Epopitin alpha in an isotonic sodium chloride/sodium citrate and administration of glucocorticoids

or IFN β (Brines et al., PNAS USA, 2000 Sept 12; 97(19):10526-10531, especially at p. 10526, column 2, second paragraph; p. 10529, column 2, second paragraph; p. 10530, column 1, second paragraph; and p. 10531, column 2, second paragraph). Brines et al., also teach that biotinylated recombinant human EPO crosses the blood-brain barrier (p. 10528, columns 1 and 2). Anti-EPOR antibodies are taught at p. 10528, column 1, first paragraph. Responsive cells, including neuronal cells, are taught at p. 10528, columns 1 and 2). EAE is taught at p. 10527, column 2, third paragraph. Inflammation resulting from glial cells are taught by the EAE models at p. 10527, column 2, third paragraph, and p. 10530, column 1, second paragraph. Inflammation triggered by apoptosis is taught at p. 10531, column 1, last paragraph to column 2, first paragraph.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

16. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 8-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brines et al., PNAS USA, 2000 Sept 12; 97(19):10526-10531, in view of Lin et al., (US Patent 5,621,080, 15 April 1997) and Satake *et al.* (Biochimica et Biophysica Acta. 1990;1038:125-129).

The claims recite as stated, *supra*. Brines et al., discloses methods of treating inflammation with a composition comprising recombinant Epoitin alpha in an isotonic sodium chloride/sodium citrate and administration of glucocorticoids or IFN β (Brines et al., PNAS USA, 2000 Sept 12; 97(19):10526-10531, especially at p. 10526, column 2, second paragraph; p. 10529, column 2, second paragraph; p. 10530, column 1, second paragraph; and p. 10531, column 2, second paragraph). Brines et al., do not teach recombinant EPO that has been modified with guanidination of the amino groups of lysine residues.

Lin teaches methods of making recombinant EPO (column 13, line 60; column 14, line 67; and Examples). Lin teaches methods of making recombinant EPO in insect cells (column 36, lines 57-61). Lin teaches methods of administering recombinant EPO to mammals (claims). Asialoerythropoietin is taught at column 5, lines 54-56). Endoglycosidase F treatment is taught at column 29, lines 12-16.

Satake et al. teach multiple embodiments of erythropoietin having at least one or more modified lysine residues or a modification of the N-terminal amino group of the erythropoietin molecule, which is highly active. Sake et al. teach that guanidination of amino groups of the lysine residues yielded derivatives that showed higher biological activities *in vitro* than native recombinant human EPO (abstract, p. 127, paragraph 4 and 5). 2,4,6,-trinitrobenzenesulfonic acid and its organic salt is taught at p. 125, column 2, last paragraph. Guanidination, amidation, carbamylation, trinitrophenylation, acetylation, succinylation, modification of arginine residues with 2,3-butanedione, nitration, and modification of carboxyl groups are taught at p. 126, column 1. Modification with phenylglyoxal is taught at p. 126, column 1; and Table 1.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of treating inflammation by administering recombinant EPO and an anti-inflammatory agent or an immunomodulatory agent to mammals as taught by Brines et al., and Lin, by modifying EPO with guanidination of the amino groups of lysine residues as taught by Satake with a reasonable expectation of success. The motivation and expectation of success is provided by Lin and Satake, in that Lin teach that recombinantly made EPO avoids the need to try to purify EPO from natural sources, which could yield unstable biologically inactive preparations of the hormone. Satake et al. teach that the guanidino groups, together with their

Art Unit: 1647

positive charges, play an important role in the interaction between the receptors and recombinant EPO.

Conclusion

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cherie M. Woodward whose telephone number is (571) 272-3329. The examiner can normally be reached on Monday - Thursday 9:00am-7:30pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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